Aldesleukin

Brand Name: Proleukin

Drug Description

Aldesleukin, a human interleukin-2 (IL-2) derivative, is a biosynthetic lymphokine. [1]

HIV/AIDS-Related Uses

Aldesleukin is not approved for the treatment of HIV; however, it has been shown to increase the CD4 cell count in HIV infected individuals.[2] Studies show that aldesleukin, in combination with antiretroviral medications, significantly increases CD4 cell counts in patients with HIV infection.[3] Results from one longitudinal study indicate that intermittent, low-frequency doses of subcutaneous aldesleukin can maintain CD4 cell increases for extended periods. The mean baseline CD4 cell count of 521 cells/microL increased to 1,005 cells/microL, and the mean baseline CD4 percent value increased from 27% to 38%, at 90 months.[4] Studies are now underway to determine whether aldesleukin, in combination with approved and investigational anti-HIV therapies and vaccines, can improve the immune system and delay the progression of HIV disease.[5] [6]

Non-HIV/AIDS-Related Uses

Aldesleukin is approved for the treatment of metastatic renal cell carcinoma and metastatic melanoma in patients 18 years and older.[7]

Pharmacology

Aldesleukin is a human recombinant interleukin-2 (IL-2) with the biologic activities of endogenous IL-2.[8] In vitro studies performed on human cell lines have revealed multiple immunological effects, including enhanced lymphocyte mitogenesis and stimulation of long-term growth of human IL-2 dependent cell lines; enhancement of lymphocyte cytotoxicity; induction of lymphokine-activated and natural killer cells; and production of cytokines, such as tumor necrosis factor, IL-1, and gamma interferon.[9] Mechanism of action studies indicate that IL-2 can induce polyclonal proliferation of CD4 and CD8 cells, even when the high-affinity IL-2 receptor is absent. Although IL-2 leads to a sixfold increase in T cell proliferation and a twofold increase in T cell death, the primary mechanism of action leading to expansion of the CD4 cell pool appears to be CD4 cell survival.[10]

After IV infusion, approximately 30% of a dose of aldesleukin is detectable in plasma. Following IV infusion over short periods, aldesleukin distributes rapidly into the extravascular space. Radiolabeled aldesleukin in rats has an uptake of less than 1 minute into the lung, liver, kidney, and spleen.[11]

In a study of HIV infected adults, aldesleukin injected subcutaneously in doses of 12, 15, or 18 million international units (MIU) per day was found to be well absorbed; however, absorption was slow, with a mean time to maximum of 4.4 hours and a lag time of 26.9 hours. Elimination half-life was 3.3 hours. A study of ultra-low dose subcutaneous aldesleukin in HIV infected adults showed marked differences in plasma concentrations. Peak plasma concentrations of aldesleukin for a subcutaneous dose of 125,000 IU/m2 were 3.4 pM, whereas doubling the dose to 250,000 IU/m2 resulted in a fivefold increase in peak plasma concentrations.[12]

Aldesleukin is in FDA Pregnancy Category C. Although there are no adequate and controlled studies in humans, aldesleukin has been shown to have embryolethal effects in rats when given in doses 27 to 36 times the usual human dose. Aldesleukin should be used during pregnancy only when the potential benefits justify the possible risks to the fetus. It is not known whether aldesleukin is distributed into human milk; however, because of the potential for serious adverse effects to the breast-fed infant if the drug is distributed into milk, discontinuation either of breast-feeding or of aldesleukin therapy should be considered.[13]

Aldesleukin is metabolized principally by the kidney; the active drug is undetectable in the urine or is present only in trace amounts. More than 80% of aldesleukin distributed to plasma, cleared from the circulation, and presented to the kidney is metabolized to amino acids in the proximal convoluted tubules. Following rapid IV infusion, elimination half-life of aldesleukin is 85 minutes.[14]

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Pharmacology (cont.)

Three mechanisms of clearance relate to the systemic removal of aldesleukin.[15] In the first two, aldesleukin is cleared from the circulation by glomerular filtration and peritubular extraction in the kidney. This dual mechanism may account for the preservation of clearance in patients with elevated serum creatinine values.[16] The third clearance pathway, an inducible receptor-mediated mechanism, was most evident in continuous IV studies in which five days of treatment in HIV infected patients resulted in a time-dependent decrease in aldesleukin serum concentrations that correlated with an increase in soluble aldesleukin receptor. The decreased aldesleukin concentrations were most likely due to induction of receptor-mediated clearance, which is related to the immunostimulatory effects of the drug. The associated decrease in aldesleukin serum levels is therefore an indicator of its activity.[17]

Because children have a faster glomerular filtration than adults, the rate of renal aldesleukin elimination in pediatric patients may be faster than in adults. Children may not have fully developed immune systems, which may affect receptor-mediated clearance.[18]

Adverse Events/Toxicity

Aldesleukin is a highly toxic drug. Adverse effects associated with aldesleukin therapy are common, often serious, and sometimes fatal. The frequency and severity of these reactions depend on dose, method of administration, and dosing schedule. Effects are generally more frequent and severe with high-dose, relatively rapid IV infusion compared with low-dose, subcutaneous administration or continuous IV infusion.[19] Subcutaneous route of administration for aldesleukin may be potentially more advantageous in HIV infected patients and may help reduce toxicity and adverse effects observed with IV aldesleukin.[20]

Aldesleukin dosages currently used in HIV clinical trials are generally lower than those used for approved indications.[21] The most commonly reported adverse effects of low to intermediate doses of aldesleukin given subcutaneously or via continuous IV infusion include asthenia; chills; diarrhea; discoloration at injection site; dry skin; fatigue; fever; headache; lethargy; loss of appetite; myalgia; nausea and vomiting; rash or inflammation at the injection site; and weight loss. Serious but rare effects include hypertension; hypotension; lung congestion; shortness of breath; and worsening of Crohn's disease, diabetes, heart failure, heart rhythm irregularities, and psoriasis.[22] [23] [24]

High-dose, rapid IV infusion of aldesleukin is FDA approved for the treatment of metastatic renal cell carcinoma and metastatic melanoma. The approved treatment is associated with severe, life-threatening effects and is therefore administered in a hospital setting.[25] These effects include capillary leak syndrome, which may be associated with cardiac arrhythmias, angina, myocardial infarction, respiratory insufficiency requiring intubation, gastrointestinal bleeding or infarction, renal insufficiency, edema, and mental status changes. High-dose aldesleukin therapy is also associated with impaired neutrophil function and with an increased risk of disseminated infection, including sepsis and bacterial endocarditis. Most adverse reactions are self-limiting and usually reverse or improve within 2 or 3 days of discontinuation of therapy. Adverse reactions that may be permanent following aldesleukin therapy may include myocardial infarction, bowel perforation or infarction, and gangrene.[26]

Drug and Food Interactions

Because aldesleukin may affect central nervous system function, interactions are possible with concomitant administration of psychotropic drugs, such as narcotics, analgesics, antiemetics, sedatives, or tranquilizers. Concurrent use of drugs causing nephrotoxic, hepatotoxic, cardiotoxic, or myelotoxic effects may increase toxicity in these organ systems. In addition, reduced kidney and liver function secondary to aldesleukin therapy may delay elimination of concomitant medications and increase the risk of adverse effects from those drugs.

Hypersensitivity reactions have been reported in patients receiving combination regimens containing sequential high dose aldesleukin and antineoplastics, specifically, cisplatinum,

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Drug and Food Interactions (cont.)

dacarbazine, and tamoxifen. Concurrent use of aldesleukin and interferon-alfa appears to increase the risk of myocardial infarction, myocarditis, severe rhabdomyolysis, and ventricular hypokinesia. This combination of agents can also cause or exacerbate autoimmune and inflammatory disorders such as bullous pemphigoid, crescentic IgA glomerulonephritis, inflammatory arthritis, oculo-bulbar myasthenia gravis, Stevens-Johnson syndrome, and thyroiditis.

Beta-blockers and other antihypertensive drugs may potentiate the hypotension associated with aldesleukin.

Although glucocorticoids have been shown to reduce some of the adverse effects of aldesleukin, including confusion, dyspnea, fever, hyperbilirubinemia, and renal insufficiency, concomitant use of these drugs with aldesleukin use may reduce aldesleukin's effectiveness and thus should be avoided.[27]

Contraindications

Aldesleukin is contraindicated in patients with a history of hypersensitivity to interleukin-2 or any component of the aldesleukin formulation. It also is contraindicated in patients with abnormal pulmonary function or thallium stress test results and in patients with organ allografts. Retreatment is contraindicated in patients who experienced the following adverse effects on prior use of the drug: sustained ventricular tachycardia (five or more beats); cardiac arrhythmias not controlled or unresponsive to management; chest pain with ECG changes consistent with angina or myocardial infarction; cardiac tamponade; intubation for longer than 72 hours; renal failure requiring dialysis longer than 72 hours; coma or toxic psychosis lasting longer than 48 hours; repetitive or difficult-to-control seizures; bowel ischemia/perforation; or gastrointestinal bleeding requiring surgery.[28]

Clinical Trials

For information on clinical trials that involve Aldesleukin, visit the ClinicalTrials.gov web site at http://www.clinicaltrials.gov. In the Search box, enter: Aldesleukin AND HIV Infections.

Dosing Information

Mode of Delivery: Intravenous infusion and subcutaneous injection.[29]

Dosage Form: Aldesleukin is available in individual single-use vials. Each vial contains 22 million IU (1.3 mg) of aldesleukin.[30] It is reconstituted by adding 1.2 ml of sterile water for injection, resulting in a final concentration of 18 million IU (1.1 mg) per ml. For rapid IV infusion, the reconstituted solution is further diluted in 50 ml of 5% dextrose injection.[31]

Storage: Store vials of lyophilized aldesleukin in a refrigerator at 2 C to 8 C (36 F to 46 F) and store in carton until time of use. Protect from light.[32] Do not shake or freeze.[33]

Chemistry

CAS Name: 125-L-Serine-2-133-interleukin 2 (human reduced)[34]

CAS Number: 110942-02-4[35]

Molecular formula: C690-H1115-N177-O203-S6[36]

Molecular weight: 15,600 daltons[37]

Physical Description: White to off-white lyophilized cake.[38]

Stability: Bacteriostatic water for injection or 0.9% sodium chloride injection should not be used for reconstitution because of increased aldesleukin aggregation.[39]

Reconstituted or diluted aldesleukin is stable for up to 48 hours at refrigerated and room temperatures, 2 to 25 C (36 to 77 F). However, the product should be refrigerated after reconstitution or dilution because it contains no preservative.[40]

Other Names

Aldesleukina[41]

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Other Names (cont.)

Interleukin-2, recombinant human[42]

rIL-2[43]

IL-2[44]

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Further Reading

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Manufacturer Information

Aldesleukin
Chiron Corp
4560 Horton Street
Emeryville, CA 94608-2916
(800) 244-7668

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Emeryville, CA 94608-2916
(800) 244-7668

For More Information

Contact your doctor or an AIDSinfo Health Information Specialist:

• Via Phone: 1-800-448-0440 Monday - Friday, 12:00 p.m. (Noon) - 5:00 p.m. ET

• Via Live Help: http://aidsinfo.nih.gov/live_help Monday - Friday, 12:00 p.m. (Noon) - 4:00 p.m. ET

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